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Synthesis of 2,3-Disubstituted Benzo[*b*]furans by the Palladium-Catalyzed Coupling of *o*-Iodoanisoles and Terminal Alkynes, Followed by Electrophilic Cyclization

Dawei Yue, Tuanli Yao, and Richard C. Larock*

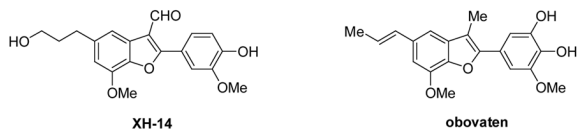
Department of Chemistry, Iowa State University, Ames, IA 50011

Abstract

2,3-Disubstituted benzo[*b*]furans are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of various *o*-iodoanisoles and terminal alkynes, followed by electrophilic cyclization using I₂, PhSeCl or *p*-O₂NC₆H₄SOCl. Aryl- and vinylic-substituted alkynes undergo electrophilic cyclization in excellent yields. Biologically important furopyridines can be prepared by this approach in high yields.

Introduction

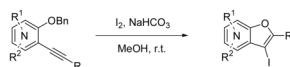
The benzo[*b*]furan nucleus is prevalent in a wide variety of biologically active natural and unnatural compounds.¹ Many 2-arylbenzofuran derivatives are well known to exhibit a broad range of biological activities, including anticancer,² antiproliferative,³ antiviral,⁴ antifungal,⁵ immunosuppressive,⁶ antiplatelet,⁷ antioxidative,⁸ insecticidal,⁹ anti-inflammatory,¹⁰ antifeedant,¹¹ and cancer preventative activity.¹² These compounds are also important calcium blockers¹³ and phytoestrogens.¹⁴ For instance, XH-14¹⁵ was the first reported potent nonnucleoside adenosine A₁ agonist¹⁶ and obovaten is known as an active antitumor agent.¹⁷



There has been growing interest in developing a general and versatile synthesis of benzo[*b*]furan derivatives. A number of synthetic approaches to this class of compounds have been introduced in recent years.¹⁸ One common approach to heterocycles that has been utilized for the synthesis of benzo[*b*]furans,¹⁹ benzo[*b*]thiophenes,²⁰ indoles²¹ and isoquinolines²² has been electrophilic cyclization of the corresponding 2-(1-alkynyl)-phenols, -thioanisoles, -anilines and -imines respectively (Scheme 1).

Our and other's recent success in this area encouraged us to examine the possibility of preparing benzo[*b*]furans by the same strategy involving a palladium/copper-catalyzed alkyne coupling, followed by electrophilic cyclization. Cacchi and co-workers have previously reported an approach to the synthesis of 3-iodobenzo[*b*]furans by a related process involving iodocyclization (Scheme 2).¹⁹ Unfortunately, the protecting and deprotecting steps required to synthesize the alkynylphenol are not particularly attractive synthetically. Some of the

alkynylphenols are also relatively unstable. In another paper, Cacchi has demonstrated an analogous cyclization of benzylic ethers to generate furopyridines and reported that the *o*-hydroxyalkynylpyridines are not stable and cyclize spontaneously to give furopyridines (eq 1).²³ We have attempted to make this overall approach more attractive synthetically by examining the preparation and cyclization of the corresponding methyl ethers using a variety of commercially available electrophiles. Herein, we wish to report an efficient approach to 2,3-disubstituted benzo[*b*]furans and furopyridines involving the palladium/copper-catalyzed coupling of various iodoanisoles and an iodomethoxy pyridine and terminal alkynes, followed by electrophilic cyclization.



(1)

Results and Discussion

The arylalkynes required for our approach to benzo[*b*]furans are readily prepared by the Sonogashira coupling²⁴ of commercially available *o*-iodoanisole (5.0 mmol) and terminal alkynes (6.0 mmol) using a catalyst consisting of 2 mol % PdCl₂(PPh₃)₂ and 1 mol % CuI in the presence of Et₃N (12.5 mL) as the solvent at room temperature. The yields of this process range from 70 to 94% and this procedure should readily accommodate considerable functionality.

We first examined the reaction of our methoxy-substituted aryl alkynes (0.25 mmol in 3 mL of CH₂Cl₂) with I₂ (2.0 equiv in 2 mL of CH₂Cl₂) under our well established reaction conditions for the synthesis of benzo[*b*]thiophenes²⁰ and indoles²¹ (Scheme 1). We were pleased to see that 2-(phenylethynyl)anisole reacted in less than 3 h at room temperature to afford 3-iodo-2-phenylbenzo[*b*]furan in an 87% yield (Table 1, entry 1). In order to extend this approach to other benzo[*b*]furans, we have also looked at a range of other readily available electrophiles. So far *p*-O₂NC₆H₄SOCl and PhSeCl have been successfully employed in this electrophilic cyclization, providing excellent yields of the desired cyclization products (Table 1, entries 2–4).

The nature of the substituents attached to the triple bond and the arene have a major impact on the success of the reaction. Virtually no difference in the rates of reaction or the overall yields have been observed using a vinylic alkyne and arylalkynes bearing certain types of functionality on the aromatic ring (entries 1–16). However, alkynes bearing an alkyl group (entries 19, 20 and 25) fail to undergo electrophilic cyclization. Instead, an almost quantitative yield of the product of simple addition of the electrophile to the alkyne triple bond was obtained (entries 19, 20 and 25). In order to form a furan moiety, the oxygen of the methoxy group has to undergo a five *endo-dig* attack on the carbon-carbon triple bond. The failure to undergo the desired cyclization in entries 19, 20, 21, 22 and 25 is possibly due to more favorable formation of a “vinylic” cation on the carbon of the triple bond next to the aryl group bearing the methoxy group, instead of on the more remote carbon (see the later mechanistic discussion). Similarly, a methoxy group *para* to the triple bond increases the electron density on the distal end of the triple bond (Figure 1), which favors electrophilic attack at that position and disfavors a five *endo-dig* cyclization. This, in turn, leads to addition of the electrophile to the triple bond, rather than cyclization (entries 17, 18 and 24).

The presence of a nitro group in compound **28** decreases the electron density on C₁ (Figure 2), and again favors simple addition of the electrophile to the alkyne triple bond (entries 21 and 22). On the other hand, the presence of an electron-withdrawing group, such as a nitro group on the methoxy-substituted arene favors electrophilic cyclization, although a longer reaction

time (12 h) is generally required (entries 11 and 12). The more electron deficient C₂ position is more likely to undergo attack by the nucleophilic oxygen of the methoxy group than the C₁ position, because of either the resonance effect of the nitro group *para* to the carbon-carbon triple bond (Figure 3) or the inductive effect of the electron-poor arene. The trimethylsilyl-substituted alkyne **29** also failed to undergo electrophilic cyclization, providing instead an inseparable mixture of unidentifiable compounds, which is consistent with Cacchi's earlier results (entry 23).¹⁹

Compound **20** with both a methoxy and an acetoxy group in positions *ortho* to the triple bond undergoes exclusive electrophilic cyclization onto the methoxy group to produce compound **21** in a 95% yield (entry 14). This should be quite useful for the regioselective synthesis of benzofurans. Thus, the more nucleophilic methoxy group more readily attacks the triple bond, affording the corresponding cyclization product.

We have also investigated the possibility of carrying out double iodocyclizations, which might be quite useful for the quick assembly of systems with extended conjugation. Compounds **22** and **24** undergo iodocyclization to afford double cyclization products in 97% and 60% yields respectively (entries 15 and 16).

While Cacchi reported the successful synthesis of several furopyridines by electrophilic cyclization of *o*-(benzyloxy)alkynylpyridines, we have examined the cyclization of an *o*-methoxyalkynylpyridine and found that a methyl group can also be a good leaving group in this reaction. Pyridine derivative **18** was treated with I₂ under our standard electrophilic cyclization conditions to afford the desired furopyridine in a 67% yield. This provides a convenient alternative route to the synthesis of furopyridines, since methoxy pyridines are more readily available than (benzyloxy)pyridines in many cases.

Mechanistically, we believe that these cyclizations proceed by *anti* attack of the electrophile and the oxygen of the methoxy group on the alkyne to produce an intermediate **A**, which undergoes methyl group removal via S_N2 displacement by nucleophiles present in the reaction mixture (Scheme 3). In most cases, the nucleophile is presumably the halide remaining in solution.

Conclusions

We believe that this approach to 3-iodobenzo[*b*]furans and furopyridines should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting iodide functionality into other substituents. For example, the resulting heterocyclic iodides should be particularly useful as intermediates in many palladium-catalyzed processes, like Sonogashira,²⁴ Suzuki,²⁵ and Heck²⁶ cross-coupling processes.

Experimental Section

General

¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or a basic KMnO₄ solution [3 g of KMnO₄ + 20 g of K₂CO₃ + 5 mL of NaOH (5%) + 300 mL of H₂O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents

All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of ethyl ether, hexanes, ethyl acetate, and CH_2Cl_2 were purchased from Fisher Scientific Co. 2-Iodoanisole, 2-bromo-1,4-dimethoxybenzene, 1-bromo-2,4-dimethoxybenzene, 2-iodo-4-nitroanisole, 2-iodo-5-nitroanisole, resorcinol, 4-iodoanisole, 1-iodo-4-nitrobenzene, phenylacetylene, 1-cyclohexenyl acetylene, 1-octyne, trimethylsilylacetylene, and Et_3N were purchased from Aldrich Chemical Co., Inc. The palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd.

General procedure for the palladium/copper-catalyzed formation of *o*-(1-alkynyl)anisoles

To a solution of Et_3N (12.5 mL), $\text{PdCl}_2(\text{PPh}_3)_2$ (2 mol %), 5.0 mmol of *o*-iodoanisole and 6.0 mol of terminal acetylene (stirring for 5 min beforehand), CuI (1 mol %) was added and stirring was continued for another 2 min before flushing with Ar. The flask was then sealed. The mixture was allowed to stir at room temperature for 3–6 h and the resulting solution was filtered, washed with satd aq NaCl and extracted with diethyl ether (2×15 mL). The combined ether fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

2-(Phenylethynyl)anisole (1)

The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 3.90 (s, 3H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.93 (t, $J = 7.6$ Hz, 1H), 7.29–7.33 (m, 4H), 7.50 (d, $J = 7.2$ Hz, 1H), 7.55–7.57 (m, 2H); ^{13}C NMR (CDCl_3) δ 56.0, 85.9, 93.6, 110.9, 112.6, 120.7, 123.7, 128.2, 128.3, 129.9, 131.8, 133.7, 160.1; IR (neat, cm^{-1}) 3058, 2926, 2855, 2226; HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{O}$ 208.0888, found 208.0894.

General procedure for the iodocyclizations

To a solution of 0.25 mmol of the alkyne and 3 mL of CH_2Cl_2 , 2 equiv of I_2 dissolved in 2 mL of CH_2Cl_2 was added gradually. The reaction mixture was flushed with Ar and allowed to stir at room temperature for the desired time. The excess I_2 was removed by washing with satd aq $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was then extracted by diethyl ether (2×10 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

3-Iodo-2-phenylbenzo[*b*]furan (2)

The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 7.28–7.51 (m, 7H), 8.16–8.19 (m, 2H); ^{13}C NMR (CDCl_3) δ 61.3, 111.4, 122.1, 123.7, 125.9, 127.7, 128.7, 129.4, 130.2, 132.7, 153.2, 154.1; IR (neat, cm^{-1}) 3058, 1450; HRMS calcd for $\text{C}_{14}\text{H}_9\text{IO}$ 319.9698, found 319.9700.

General procedure for the *p*- $\text{O}_2\text{NC}_6\text{H}_4\text{SCl}$ and PhSeCl cyclizations

To a solution of 0.25 mmol of the alkyne and CH_2Cl_2 (5 mL), 0.375 mmol of *p*- $\text{O}_2\text{NC}_6\text{H}_4\text{SCl}$ or PhSeCl was added. The mixture was flushed with Ar and allowed to stir at 25 °C for 2–6 h. The reaction mixture was washed with 20 mL of water and extracted with diethyl ether. The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was further purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-Phenyl-3-(phenylselenyl)benzo[*b*]furan (3)

The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 7.13–7.17 (m, 3H), 7.22 (t, J = 4.0 Hz, 1H), 7.27–7.32 (m, 4H), 7.43 (t, J = 7.6 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 8.19–8.21 (m, 2H); ^{13}C NMR (CDCl_3) δ 99.9, 111.4, 121.4, 123.6, 125.4, 126.4, 128.0, 128.7, 129.4, 129.5, 130.3, 131.6, 132.1, 154.3, 157.4; IR (neat, cm^{-1}) 3058, 2926; HRMS calcd for $\text{C}_{20}\text{H}_{14}\text{OSe}$ 350.0211, found 350.0220.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Figure 1.
Methoxy electron-donating effect on the triple bond

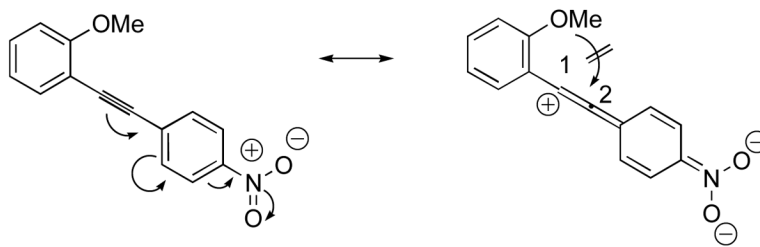


Figure 2.
Nitro electron-withdrawing effect on the triple bond

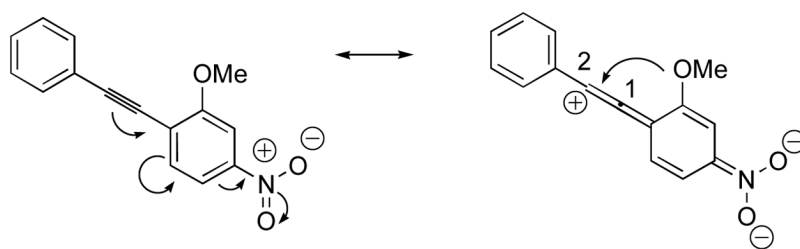
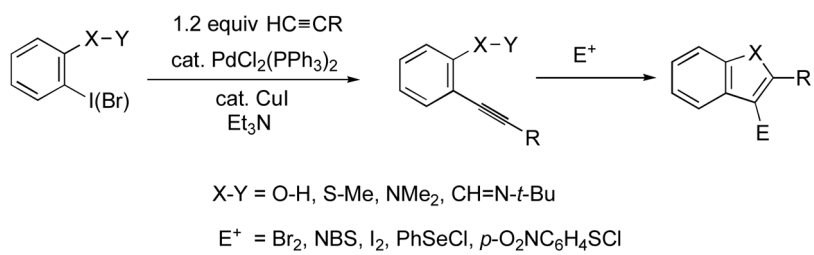
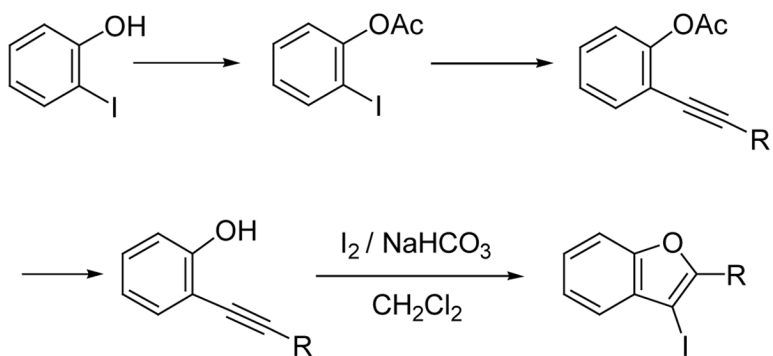
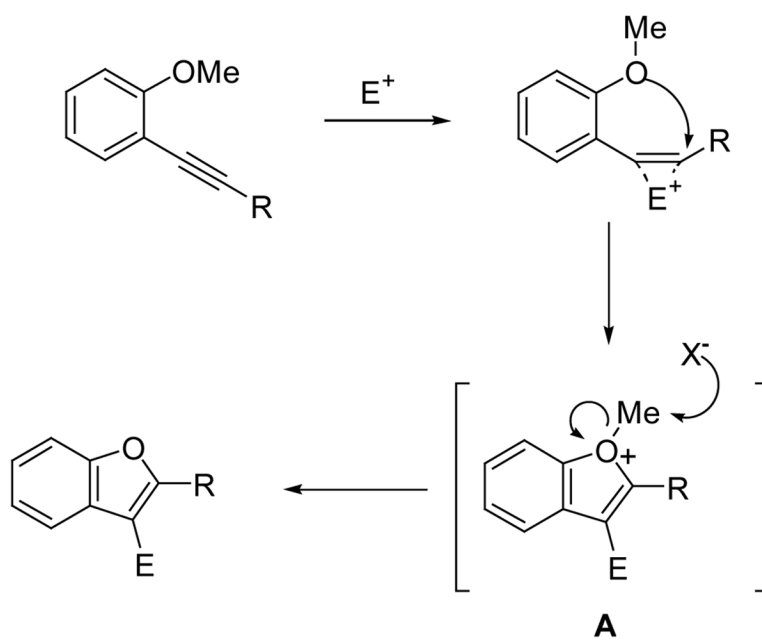


Figure 3.
Nitro electron-withdrawing effect on the triple bond

**Scheme 1.**

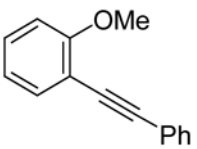
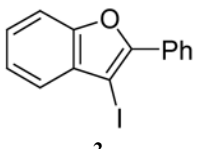
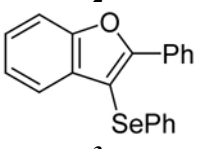
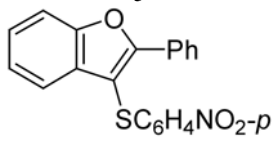
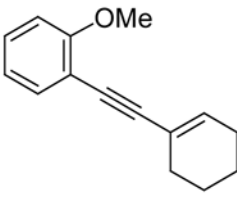
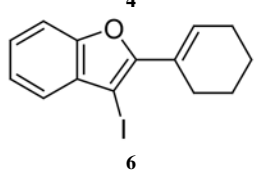
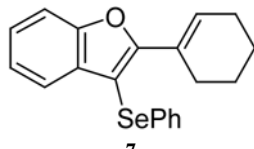
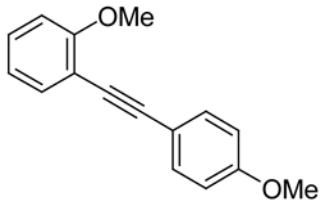
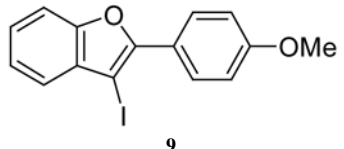
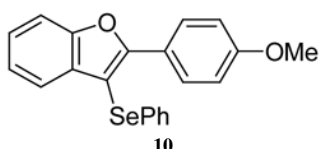
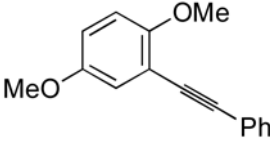
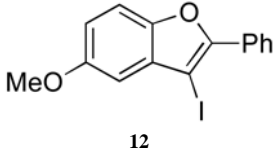


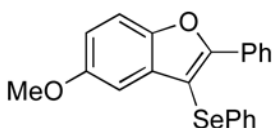
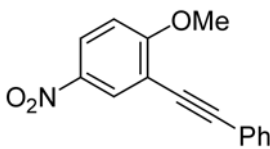
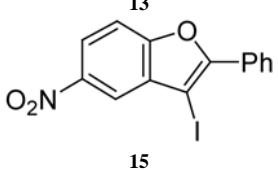
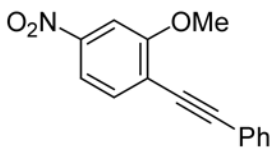
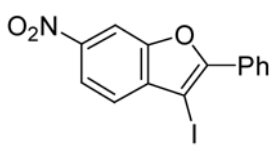
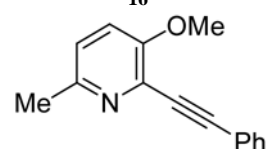
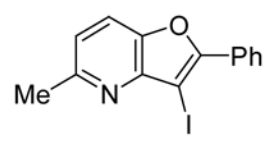
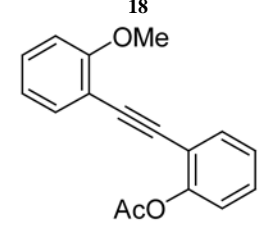
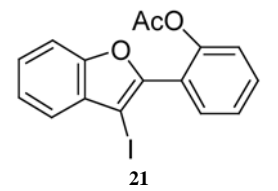
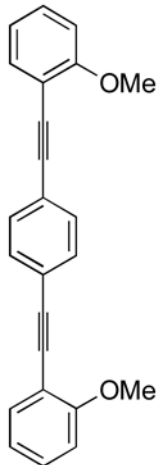
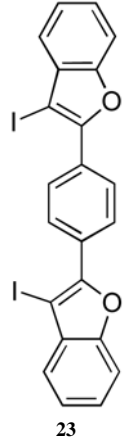
Scheme 2.

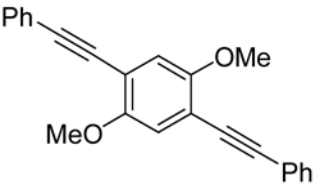
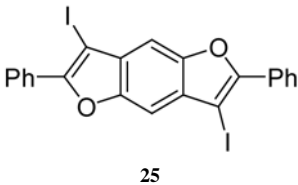
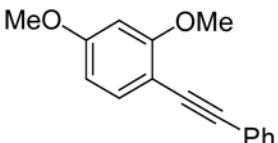
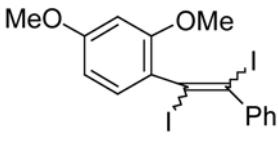
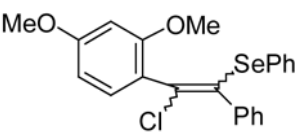
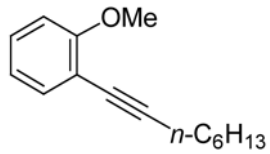
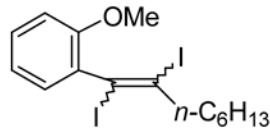
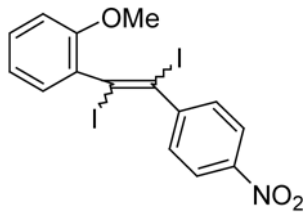
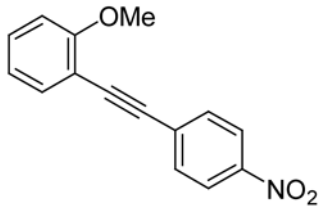
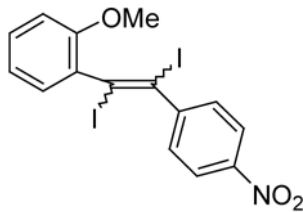
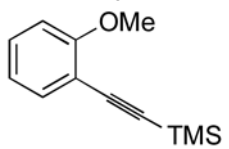
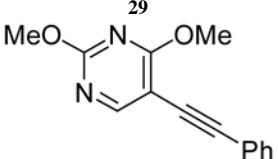
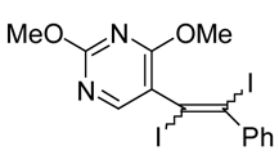
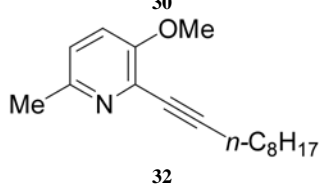
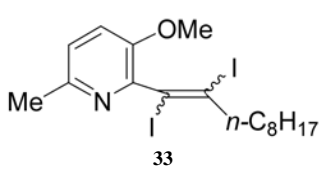


Scheme 3.

Table 1
Synthesis of benzo[*b*]furans by electrophilic cyclization.^a

entry	alkyne	electrophile	product	% yield
1		I ₂		87
2	1	ICl	2	98
3	1	PhSeCl		100
4	1	<i>p</i> -O ₂ NC ₆ H ₄ SCl		85
5		I ₂		80
6	5	PhSeCl		88
7		I ₂		100
8	8	PhSeCl		96
9		I ₂		74

entry	alkyne	electrophile	product	% yield
10	11	PhSeCl		90
11		I ₂	13 	80 ^b
12		I ₂	17 	67 ^b
13		I ₂	19 	67 ^b
14		I ₂	21 	95
15		I ₂	23 	97

entry	alkyne	electrophile	product	% yield
16	 24	I ₂	 25	60
17	 26	I ₂		66 ^c
18	26	PhSeCl		80 ^c
19	 27	I ₂		98 ^c
20	27	PhSeCl		^c
21	 28	I ₂		^d
22	28	PhSeCl		^d
23	 29	I ₂		^d
24	 30	I ₂	 31	68
25	 32	I ₂	 33	66

^a All reactions were run with 0.25 mmol of the alkyne, 2 equiv of electrophile in 5 mL of CH₂Cl₂ at 25 °C for 3 h.

^bThe reaction took 12 h.

^cNone of the desired cyclization product was observed.

^dAn inseparable mixture was obtained.